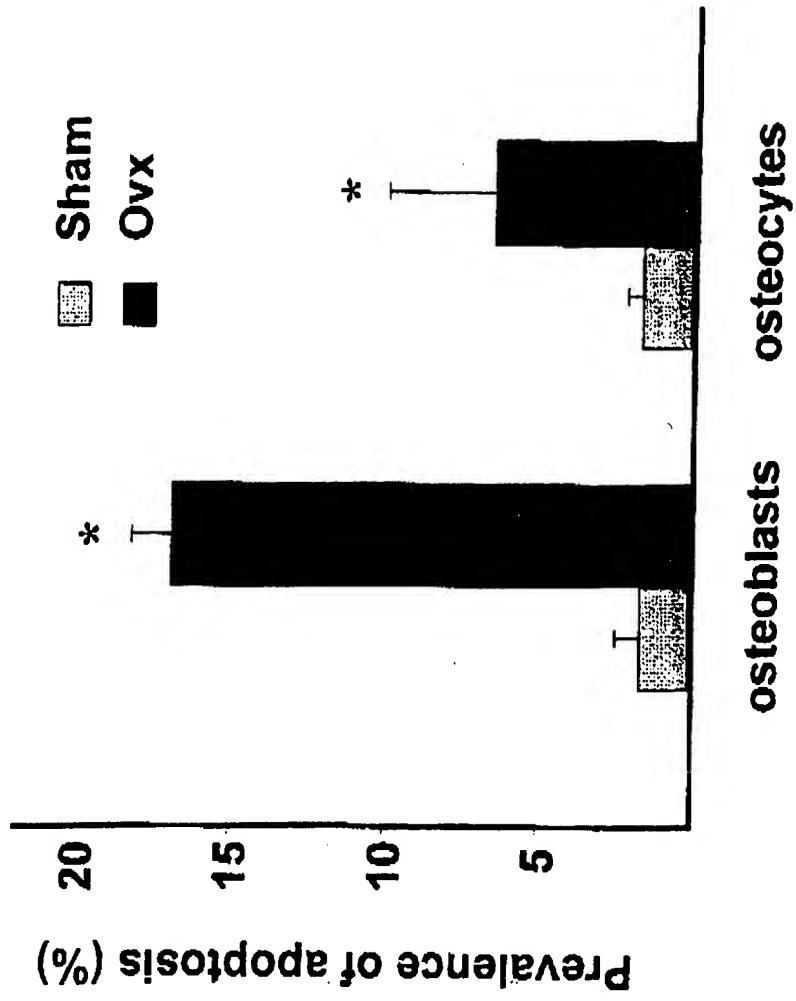
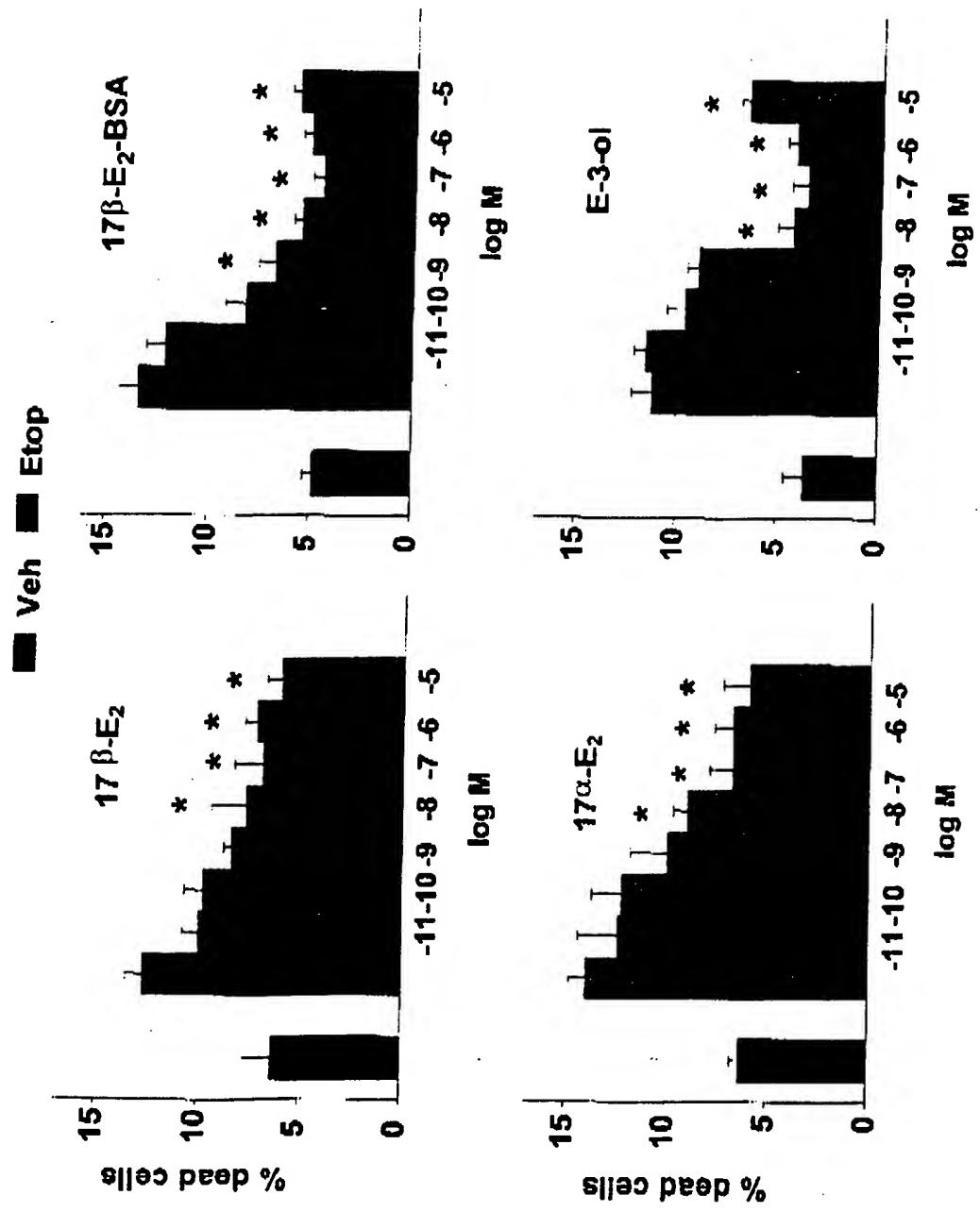


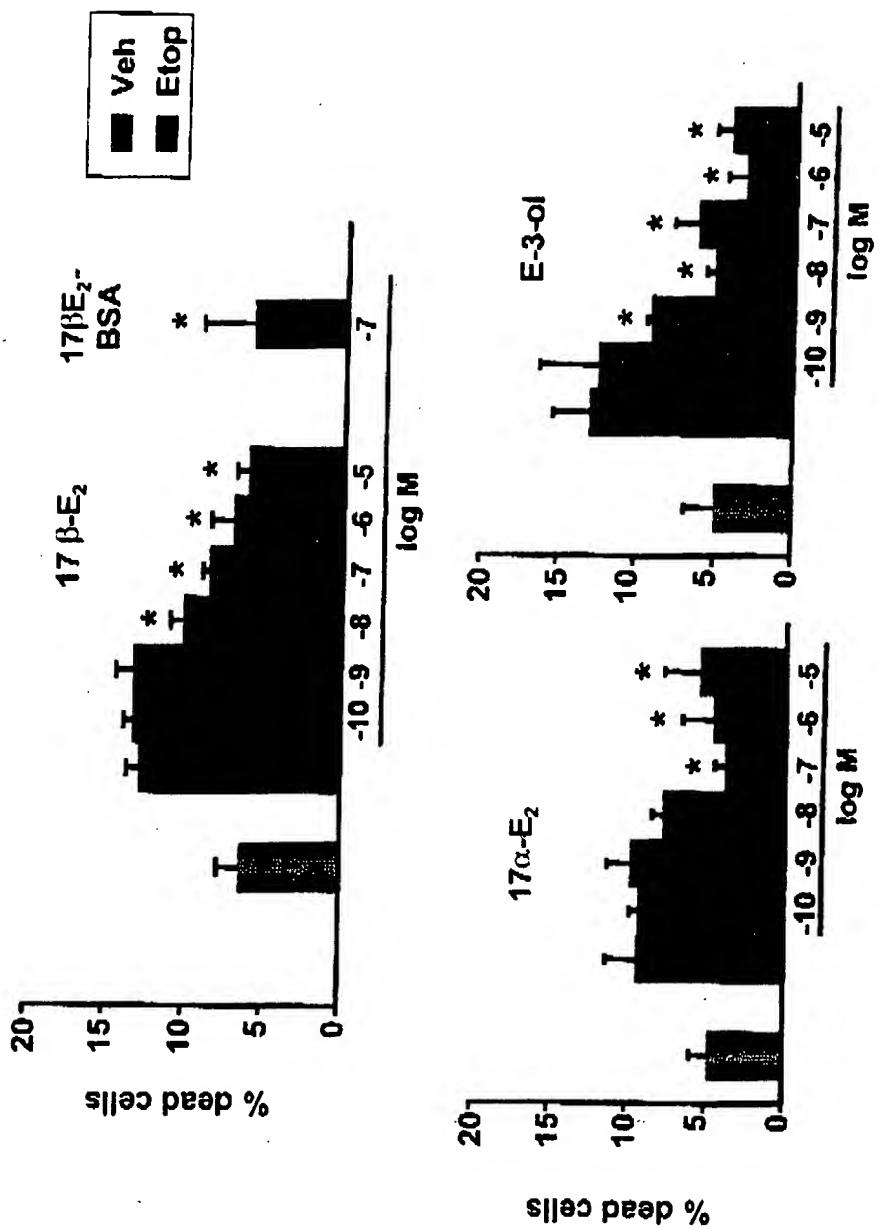
**Figure 1:** General structure of activators of non-genomic Estrogen-Like Signalling (ANGELS).



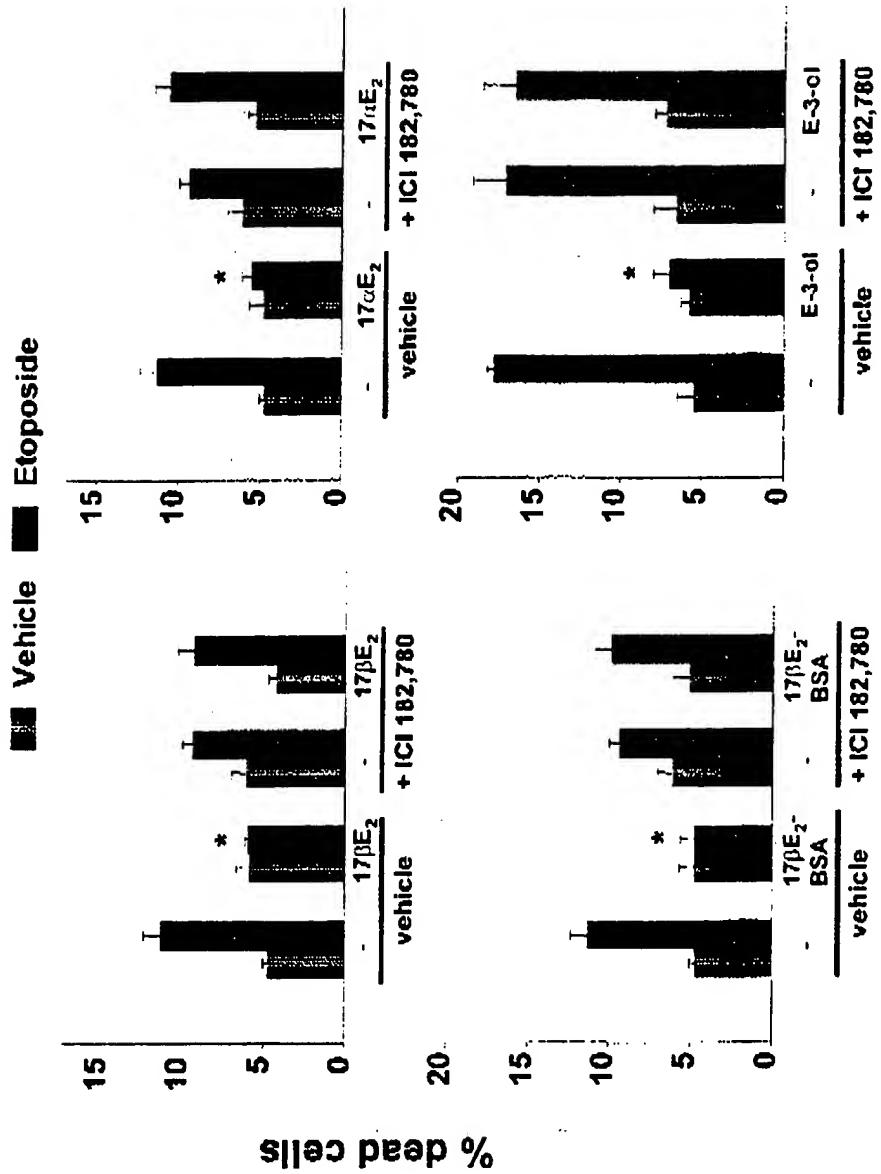
**Figure 2:** Estrogen deficiency causes increased apoptosis of osteoblasts and osteocytes in murine vertebral bone.



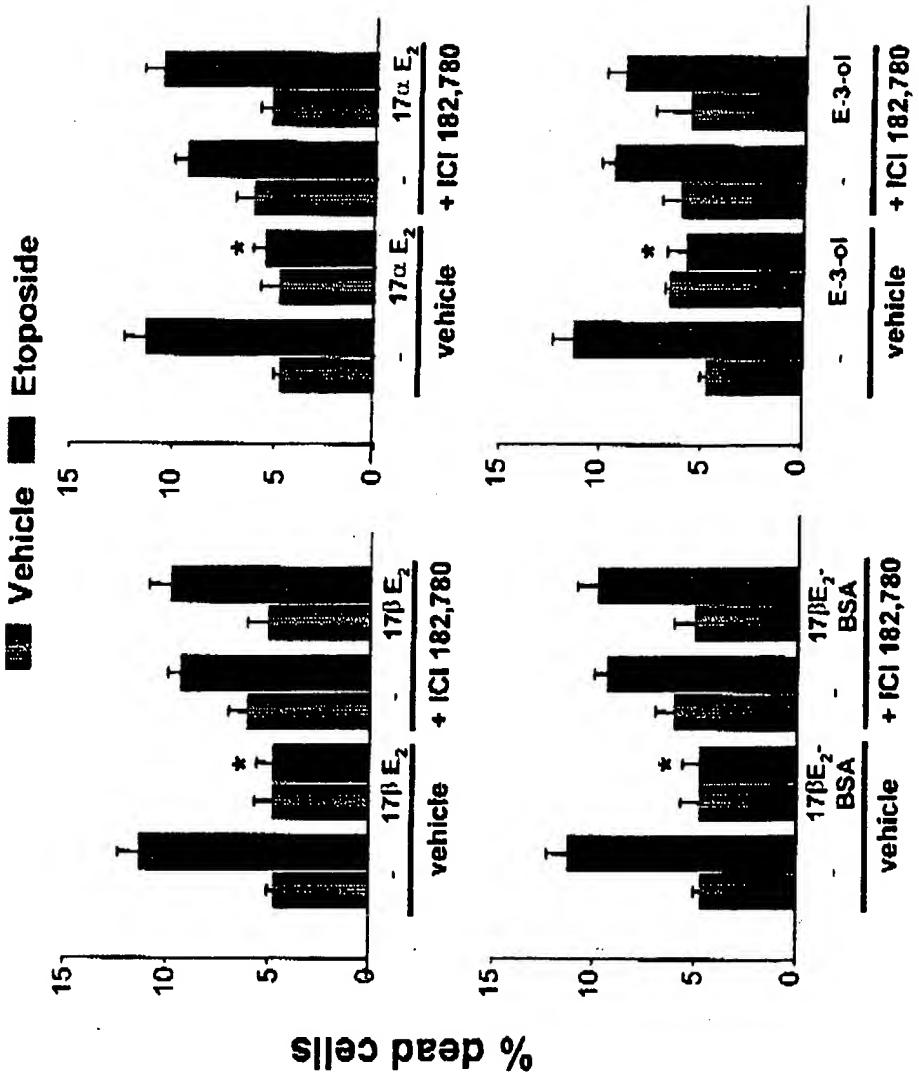
**Figure 3: Inhibition of apoptosis of osteoblastic cells.**



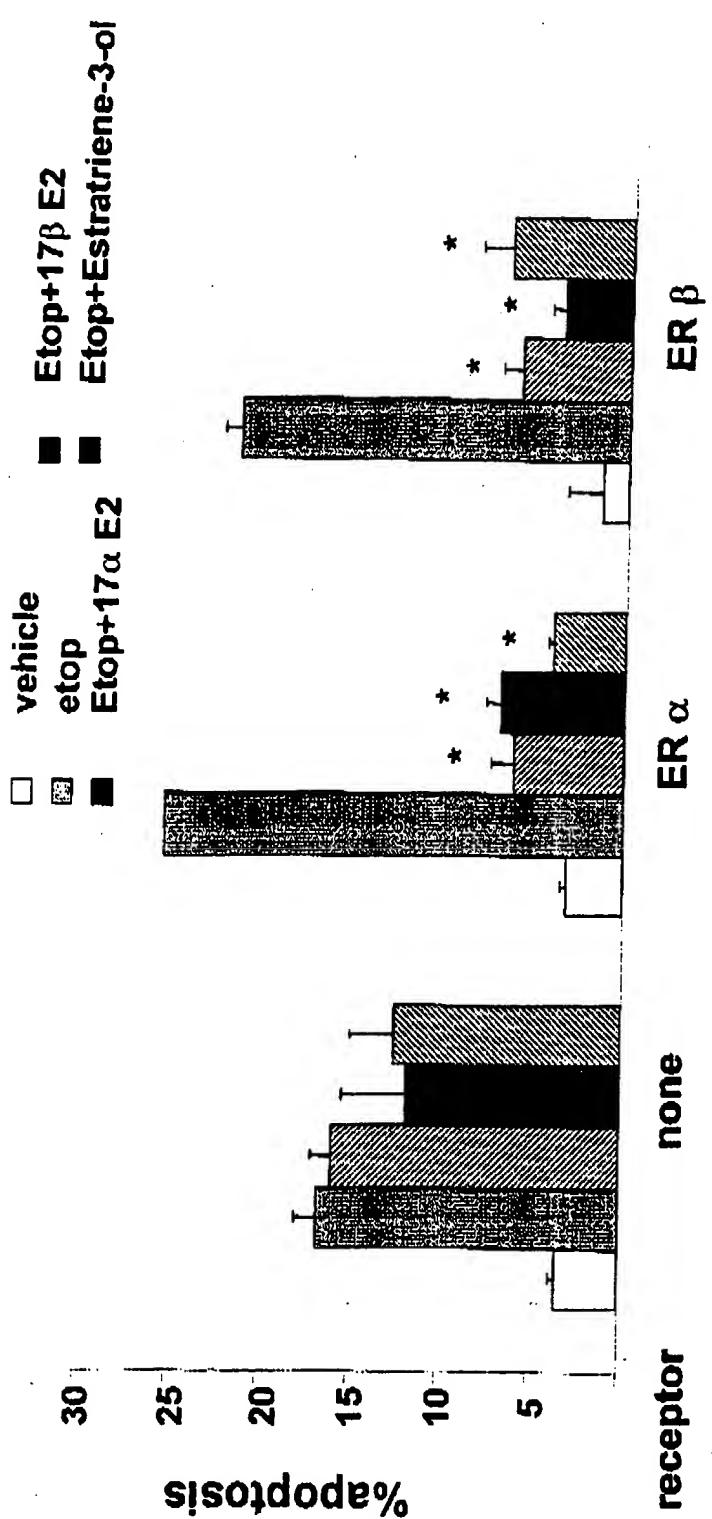
**Figure 4: Inhibition of apoptosis of MLO-Y4 osteocytic cells by ANGELS**



**Figure 5: Blockade of the anti-apoptotic effect of estrogen and ANGELS by ICI 182,780 in osteoblastic cells**

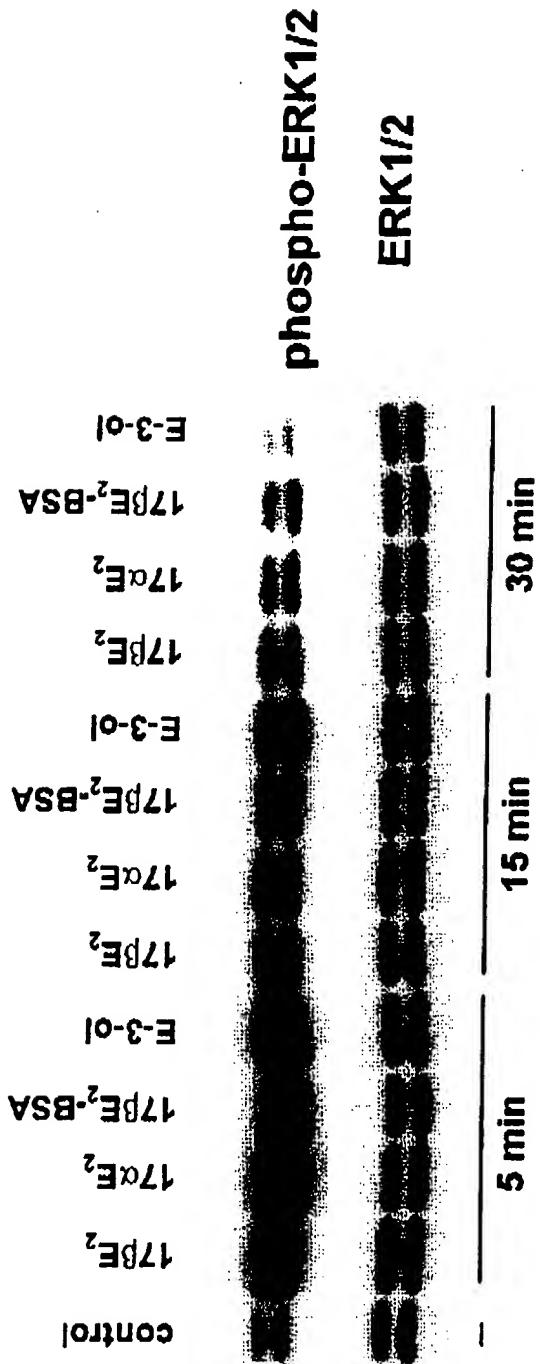


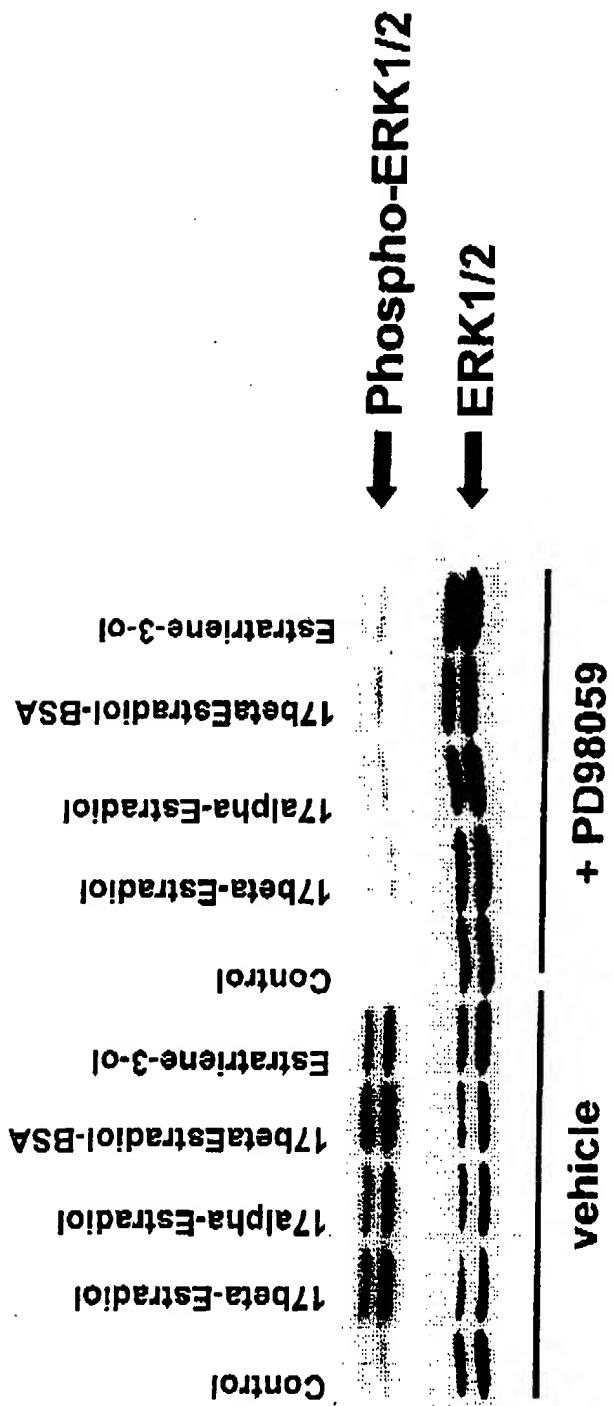
**Figure 6: Inhibition of the antiapoptotic effect of estrogen and ANGELS by ICI 182,780 in MLO-Y4 osteocytic cells**



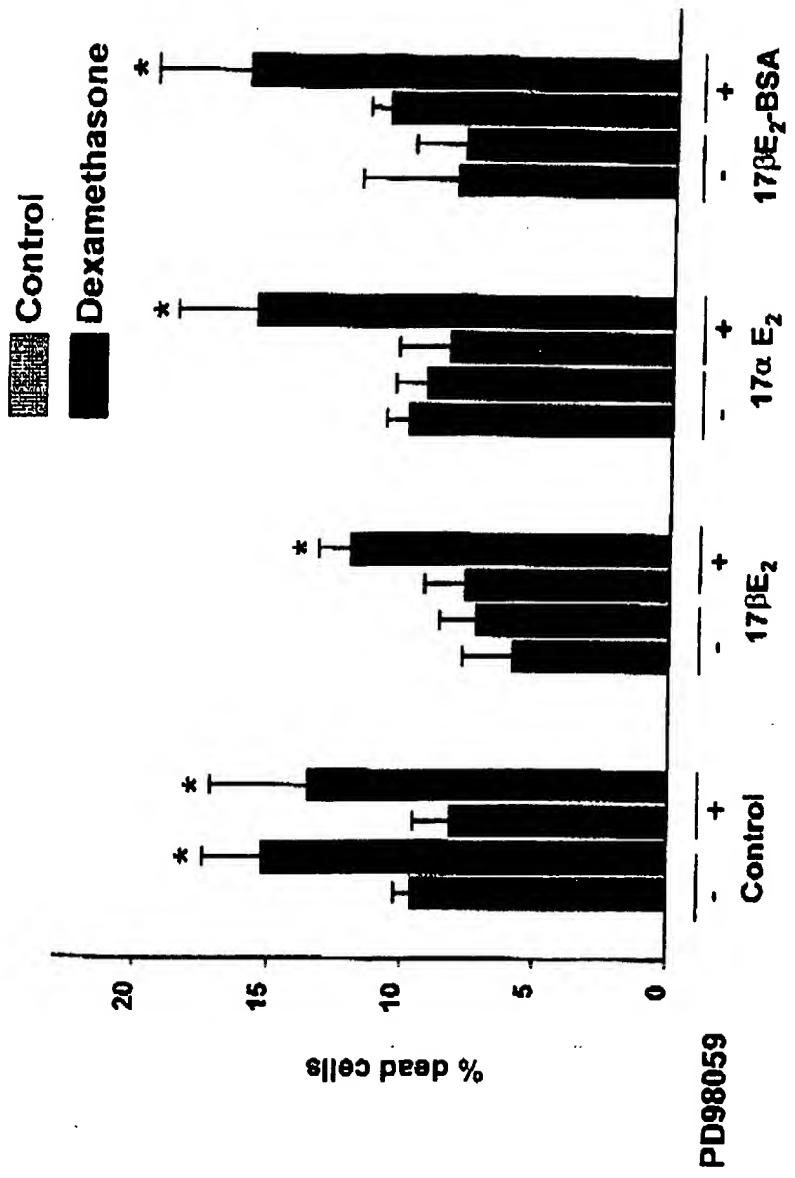
**Figure 7:** Estrogen receptor  $\alpha$  or  $\beta$  is required for the antiapoptotic effects of 17 $\beta$  estradiol, 17 $\alpha$  estradiol, and estratriene-3-ol on etoposide-induced apoptosis (experiment 1/21/99).

**Figure 8: Activation of Extracellular Signal Regulated Kinases (ERKs)**

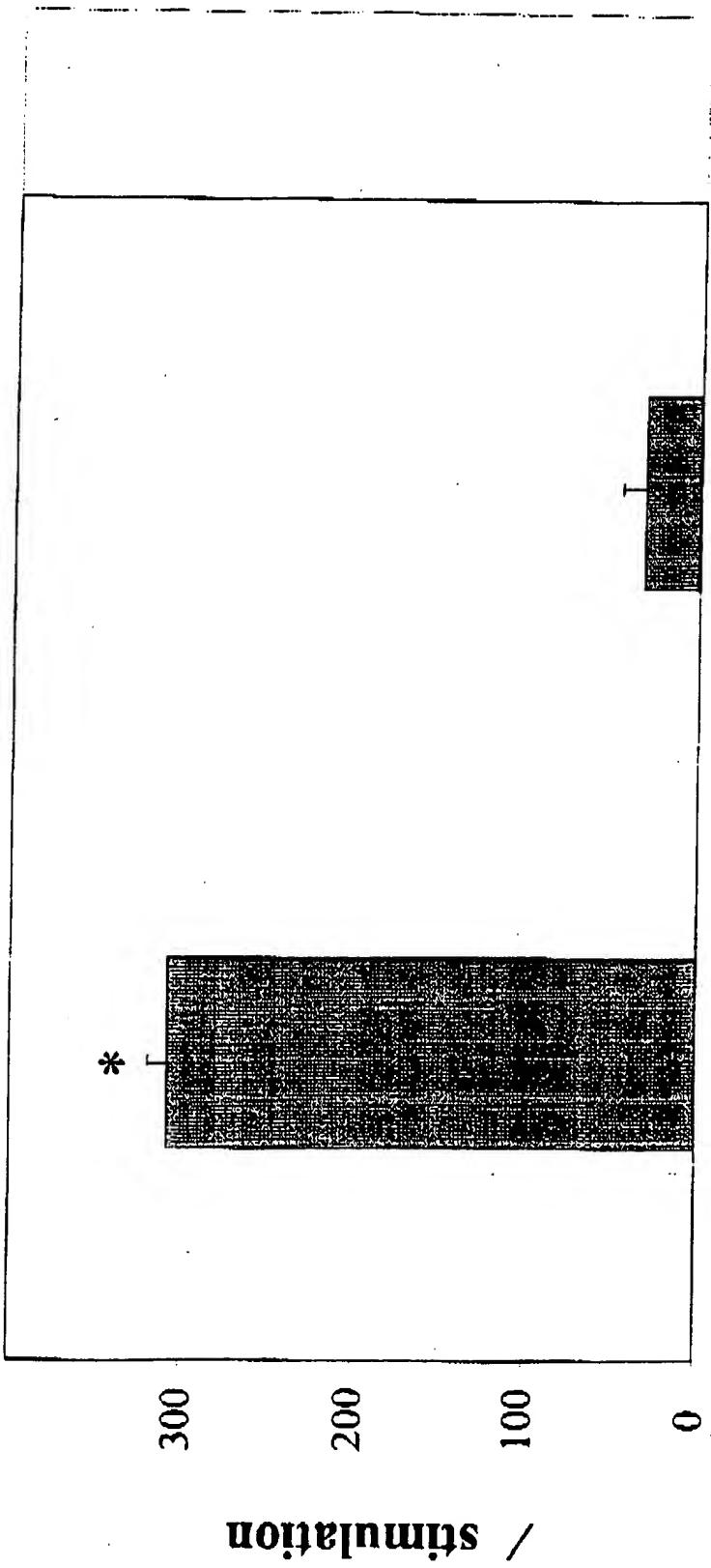




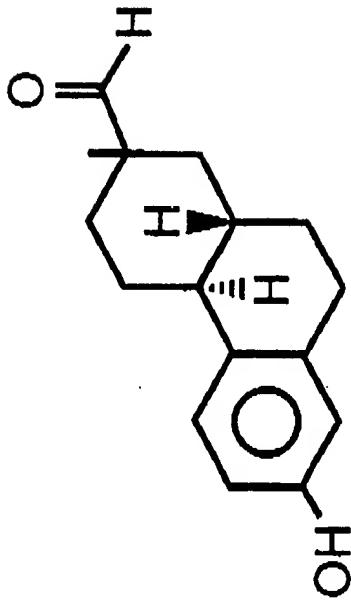
**Figure 9:** The effect of estrogenic compounds on the activation of ERK1/2 is blocked by a specific inhibitor.



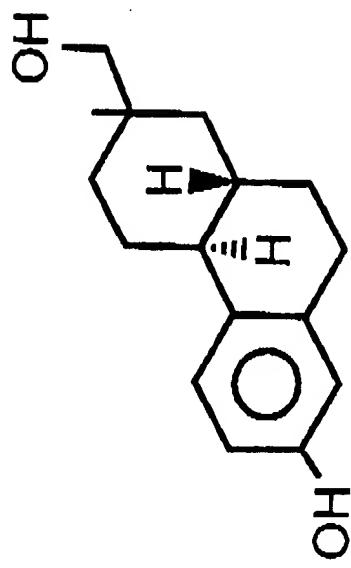
**Figure 10:** The specific inhibitor of ERK activation abolishes the anti-apoptotic effect of the estrogenic compounds.



**Figure 11:** Unlike 17 $\beta$  estradiol, estratriene-3-ol does not transactivate an estrogen response element through ER $\alpha$ .



[2S-(2a,4ac,10af)]-1,2,3,4,4a,9,10,10a-  
Octahydro-7-hydroxy-2-methyl-2-  
phenanthrenecarboxaldehyde

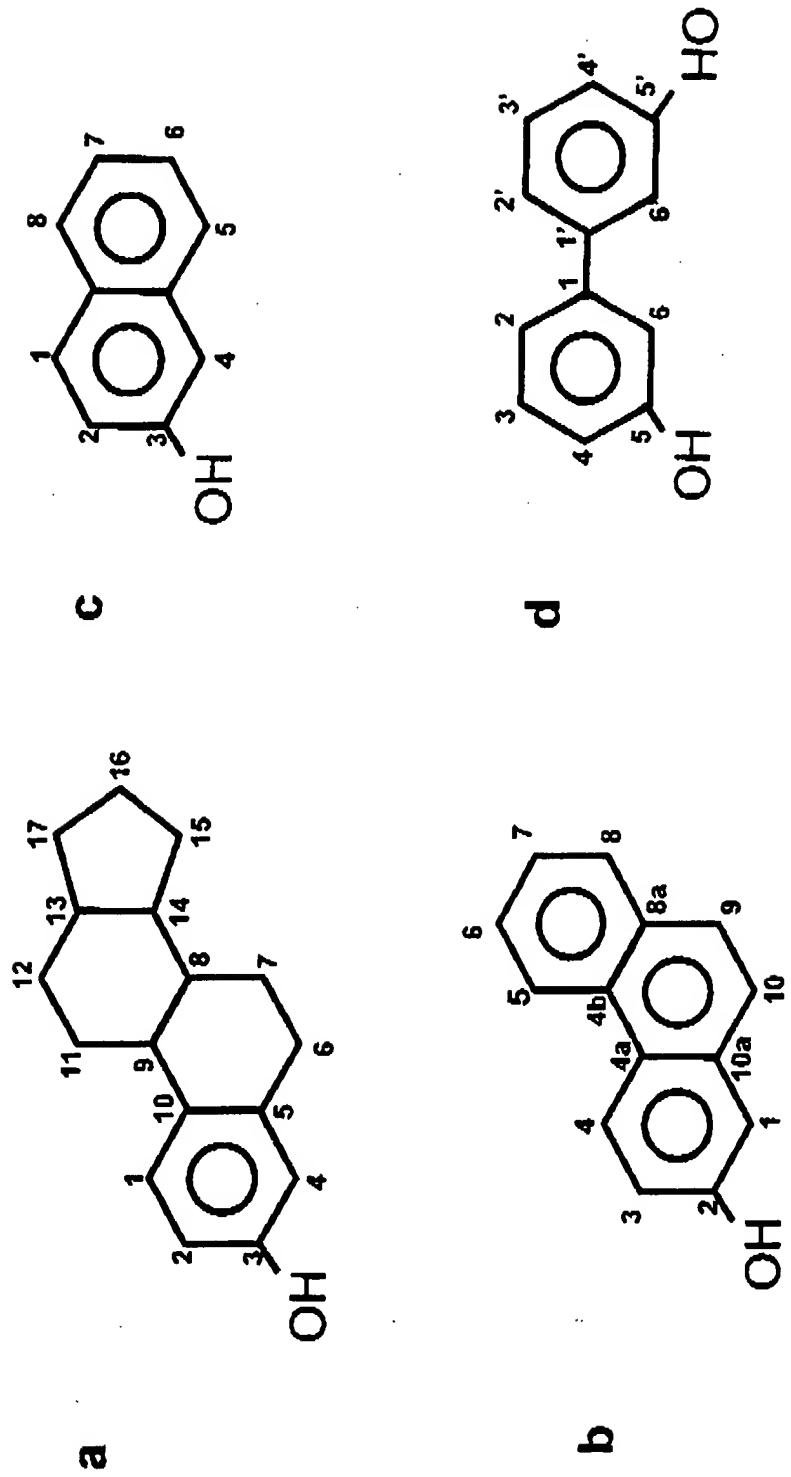


C<sub>16</sub>H<sub>22</sub>O<sub>2</sub>  
MW=246

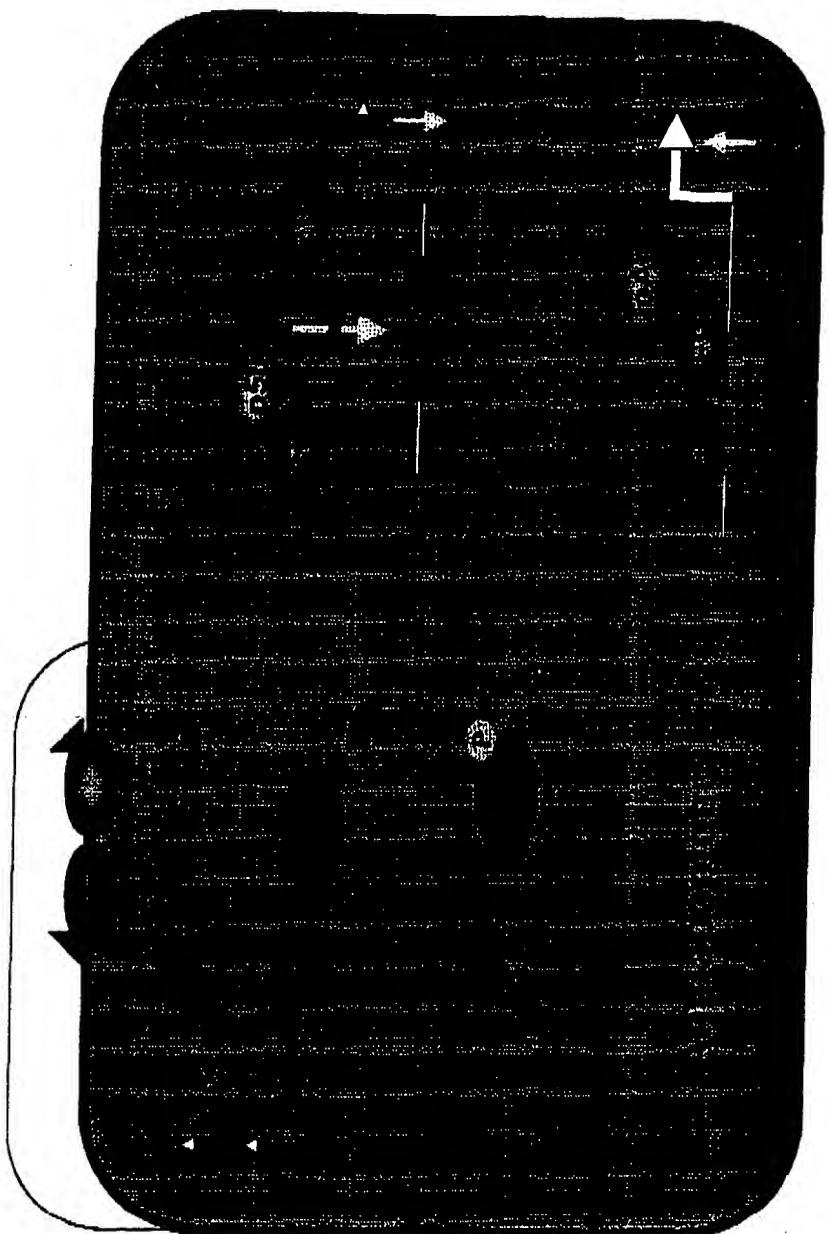
[2S-(2a,4ac,10af)]-1,2,3,4,4a,9,10,10a-  
Octahydro-7-hydroxy-2-methyl-2-  
phenanthrenemethanol

**Figure 12**

Figure 13

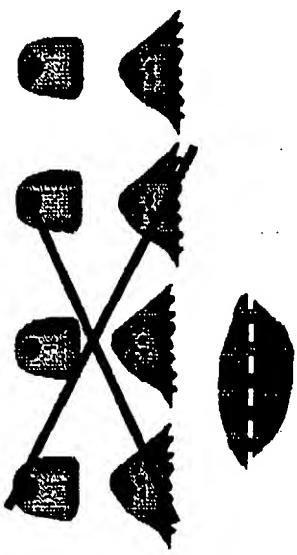


**Figure 14: Mechanisms of Estrogen Receptor Action**

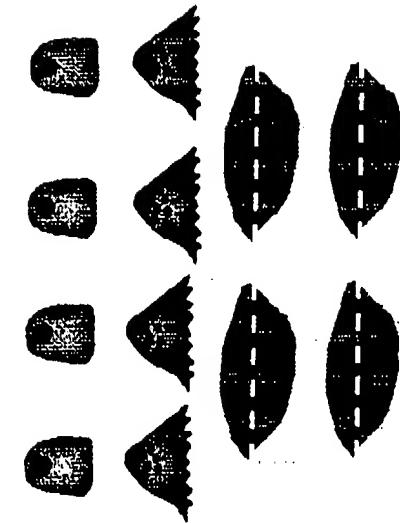


**Formation occurs only on sites of previous osteoclastic bone resorption.**

**Anti-resorptive**



**Non anti-resorptive (i.e. ANGELS)**



**Small and slow increase  
in trabecular thickness**

**Large and rapid increase  
in trabecular thickness**

**Anti-fracture efficacy  
(through inhibition of osteocyte apoptosis)**

**Figure 15:** Implications of the effects of anti-resorptive vs. non anti-resorptive agents on apoptosis

R AND/OR R' SUBSTITUTION	
	STRUCTURE
HCO <sub>2</sub>	-OH
Et <sup>+</sup>	-CH <sub>3</sub>
METHYL E <sup>+</sup>	-OCH <sub>3</sub>
AC <sup>+</sup>	O-C(=O)-CH <sub>3</sub>
ETHYL ET <sup>+</sup>	O-CH <sub>2</sub> -CH <sub>3</sub>
3, 3, 3, FOR 1 <sup>+</sup> DIMETHYL E <sup>+</sup>	OCH <sub>3</sub> OCH <sub>3</sub>
ETHY-	C≡CH CH <sub>3</sub>
BENZ <sup>+</sup>	O-C(=O)-C <sub>6</sub> H <sub>5</sub>
BENZYL ET <sup>+</sup>	OCH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>
GLUCURONIC ACID	C <sub>6</sub> H <sub>8</sub> O <sub>6</sub>
SULFATE SODIUM :	OSO <sub>3</sub> Na
C <sup>+</sup>	=
VAL <sup>+</sup>	-C <sub>5</sub> H <sub>8</sub> C
CYCLOPENTYLPROPI <sup>+</sup>	-O-C(=C)-C <sub>5</sub> H <sub>9</sub>
PROPI <sup>+</sup>	-O-C(=C)-CH <sub>2</sub> CH <sub>3</sub>
HEMISUCC <sup>+</sup>	-C <sub>4</sub> H <sub>6</sub> O <sub>3</sub>
PAL <sup>+</sup>	-C <sub>16</sub> H <sub>32</sub> O <sub>2</sub>

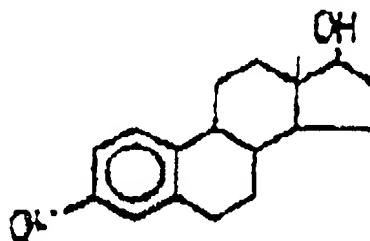
Figure 16A

R<sub>1</sub> AND/OR R<sub>2</sub> SUBSTITUTIONS

	STRUCTURE
SODIUM PHOSPHENANTH	-O-PO <sub>3</sub> Na <sub>2</sub>
GLUCURONIDE SODIUM S-	-C <sub>6</sub> H <sub>8</sub> O <sub>3</sub> Na
STEAP	-C <sub>18</sub> H <sub>34</sub> O
TRETHYL AMMONIUM S-	-N-(C <sub>2</sub> H <sub>5</sub> ) <sub>3</sub>
CYPIC	

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17B EST...



17a EST...

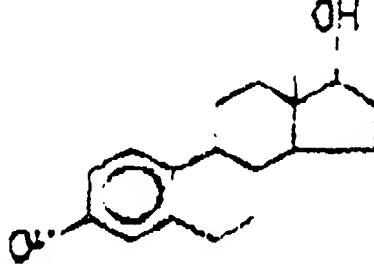
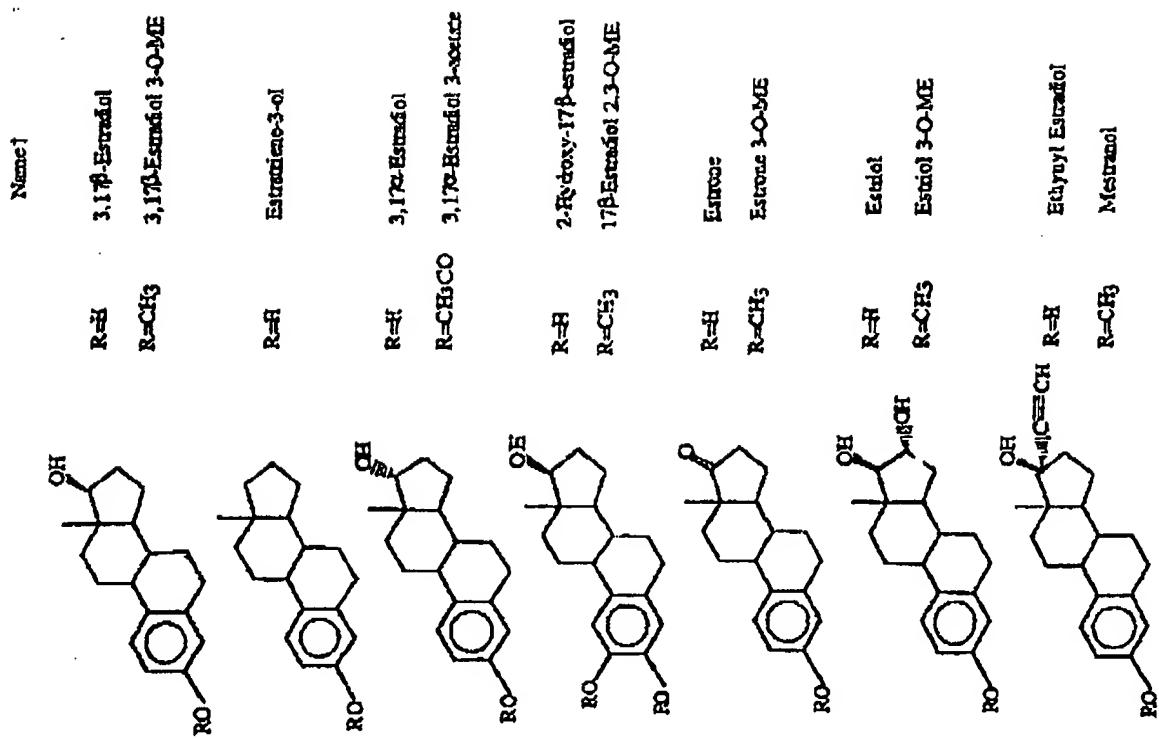
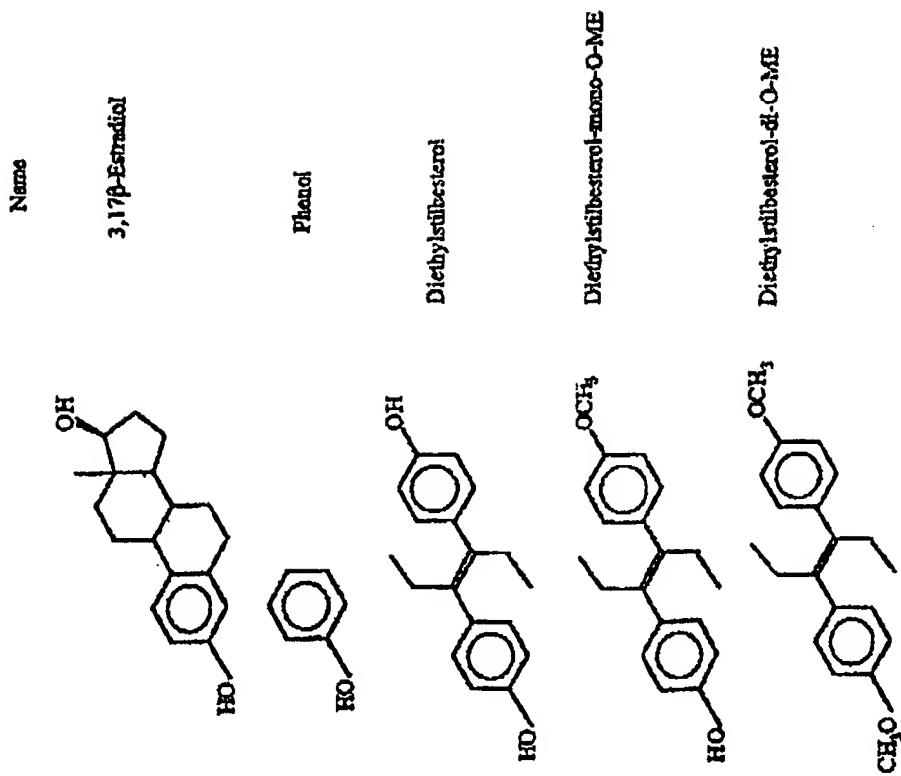


Figure 16B

Figure 17





**Figure 18**

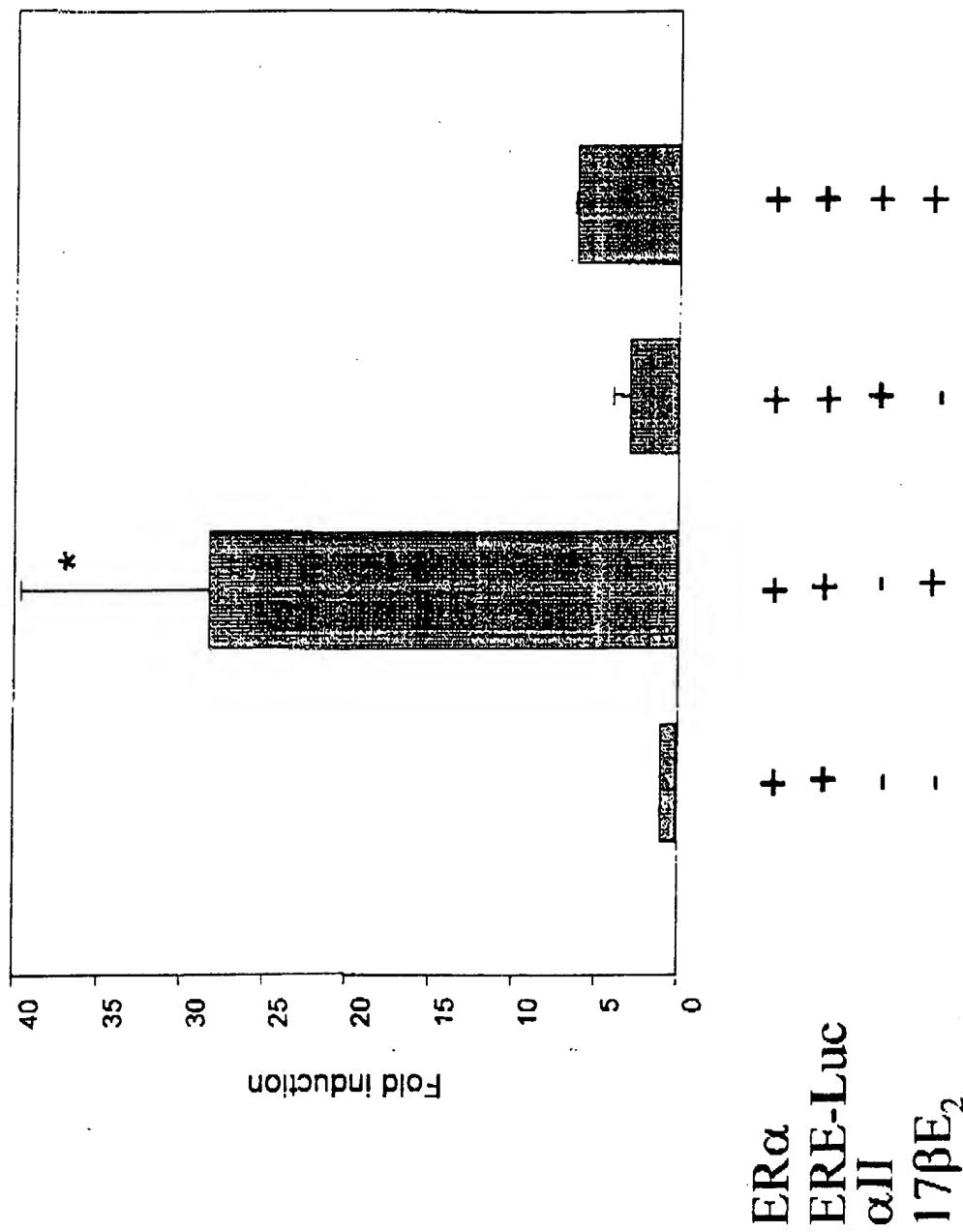
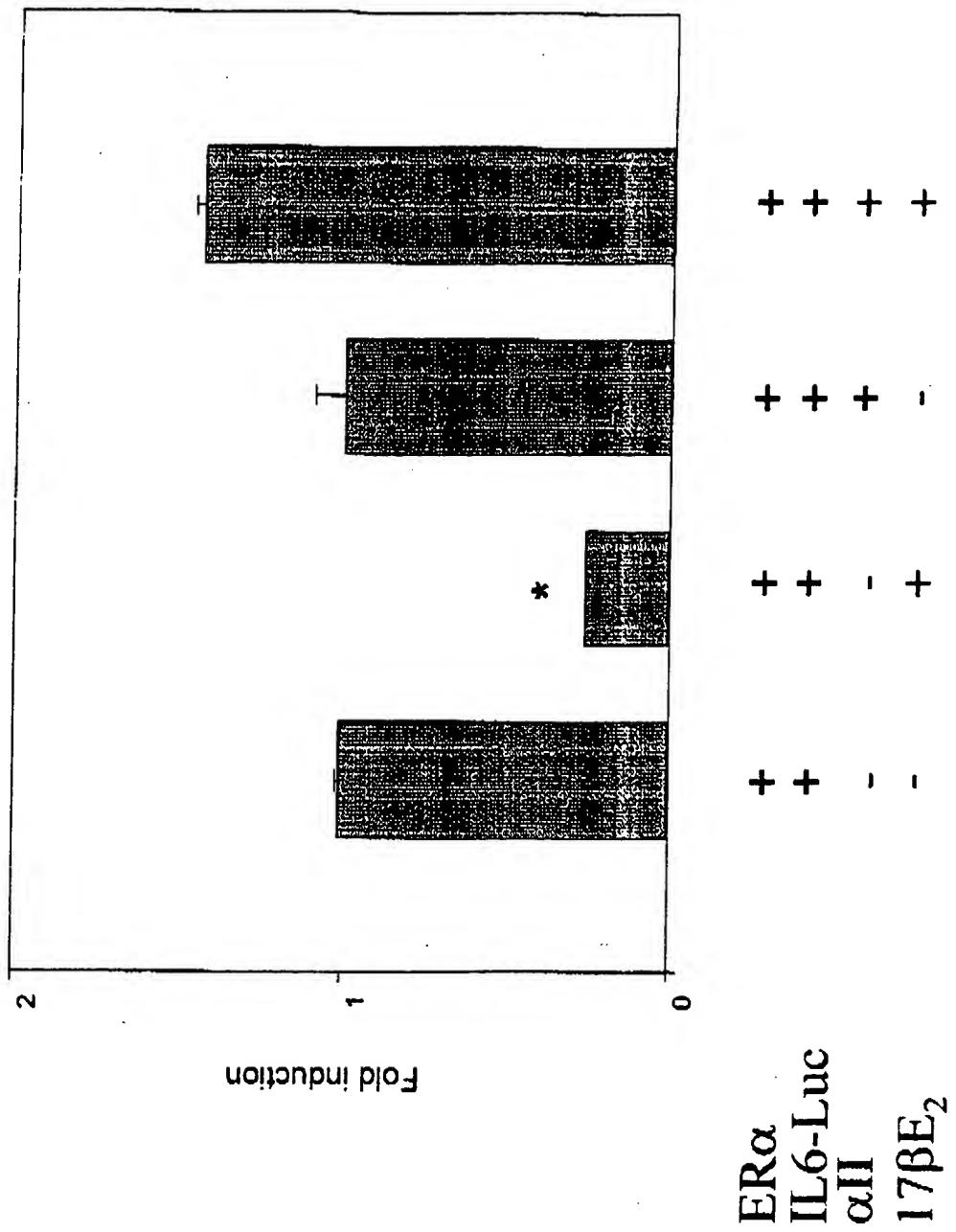
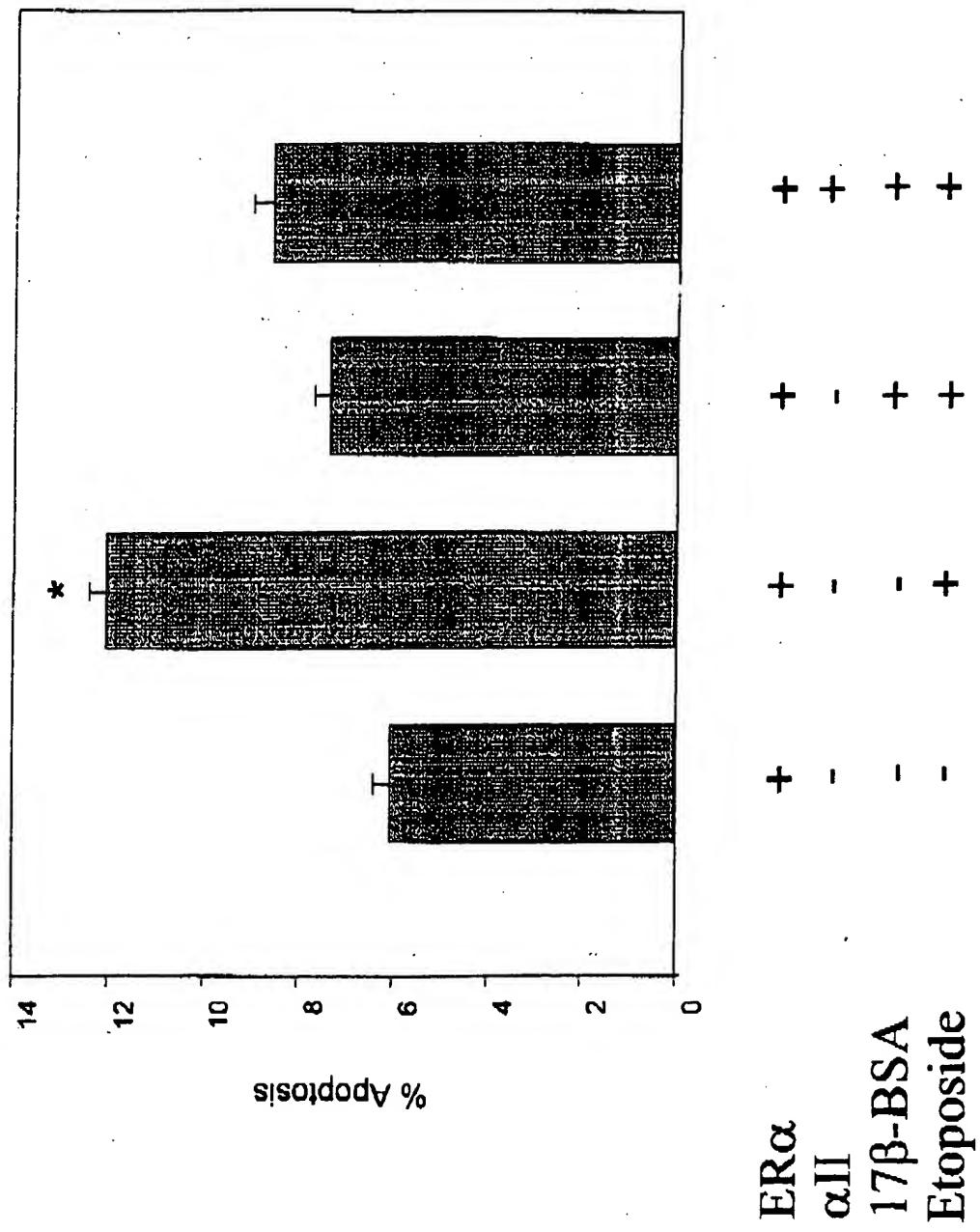


Figure 19: Effect of the all peptide on the 17 $\beta$ E $_2$ -induced ERE activity in 293 cells



**Figure 20:** Effect of the all peptide on the 17 $\beta$ E $_2$ -induced inhibition of IL-6 activity in 293 cells



**Figure 21:** Effect of the all peptide on the Etoposide-induced apoptosis of 17 $\beta$ -BSA-activated 293 cells